REMARKS

Claims 1-14 are pending. Claims 11-12 are rejected under 35 U.S.C. § 101. Claims 1-4, 6-8, and 8-14 were rejected under 35 U.S.C. § 102(b). Claims 1-5 and 8-9 were rejected under 35 U.S.C. § 103(a). Each of these rejections is addressed below.

Claim Amendments

Claims 1 and 8 have been cancelled. Claim 9 has been cancelled as well, with its features being incorporated into claim 2.

Claim 2 has been amended to require (i) contacting a Sendai virus vector with an immature dendritic cell or (ii) contacting a Sendai virus vector with a precursor cell of a dendritic cell to cause the precursor cell to differentiate into an immature dendritic cell, wherein the immature dendritic cell of (i) or (ii) undergoes maturation thereby producing a mature dendritic cell. Support for this amendment is found in the specification, for example, on page 16, lines 13-31. As is discussed below, an immature dendritic cell containing Sendai virus vector is automatically maturated, accordingly, achieving production of a mature dendritic cell.

Claims 3-5 have been amended for consistency with the amendment of claim 2. The phrase "$CD11c^+$ cell" as found in amended claim 4 is supported by the specification, for example, the passage found on page 16, lines 13-15.

Claim 11 has been amended to include the term "mature" in accord with amended claim 2. The term "isolated" has also been included.

Claim 12 has been canceled.

New claims 15 and 16 are based on applicants' disclosure found on page 24, lines 4-5 (*"Viral vectors of this invention are capable of encoding foreign genes in their genomic RNA"*).

New claim 17 is based on claim 6, and page 35, lines 11-12 (*"Moreover, when an antigen peptide is expressed in dendritic cells using the vector of the present invention, the cells presenting this peptide can be used as a vaccine"*).

New claims 18 and 19 are based on claims 7 and 10, respectively.

New claim 20 finds support in the specification, for example, on page 16, lines 13-31.

New claims 21-23 find support in the specification, for example, page 14, lines 12-13 and page 16, lines 13-15 in combination with Experiment 6 (page 46) and Experiment 1 (page 46).

No new matter has been added by any of these amendments.

Applicants reserve the right to pursue any cancelled subject matter in this or a continuing application.

Claim Rejections - 35 U.S.C. § 101

Claims 11-12 were rejected under 35 U.S.C. § 101 on the ground that the claimed invention is directed to non-statutory subject matter. The examiner notes that insertion of the term "An isolated" to modify the phrase "vector-comprising cell" would overcome the rejection. In view the present amendment to these claims, this rejection should be withdrawn.

Claim Rejections - 35 U.S.C. § 102(b)

Claims 1-3 and 10-14 were rejected under 35 U.S.C. § 102(b) as anticipated by Steinman et al. (US 6,300,090). Claims 1-3, 6-8, and 10-14 were rejected under 35 U.S.C. § 102(b) as anticipated by Song et al. (US 2002/0123479 A1). In response, applicants note that the claims, as amended, incorporate the feature of claim 9, which is free of each rejection. These grounds of rejection should therefore be withdrawn. Furthermore, claim 1 has been canceled.

Claims 1-2, 4, and 8-11 were rejected under 35 U.S.C. § 102(b) as being anticipated by Jin et al. (*Gene Therapy* 10:272-277, February 2003) as evidenced by Romani et al. (*J. Exp. Med.* 180:83-93, 1994). As the Office points out, Jin discloses "a method in which recombinant Sendai virus is in contact and provides a highly efficient gene transfer into human cord blood $CD34^+$ cells." The Office further notes that human cord blood $CD34^+$ includes at least $CD34^+$ precursor cells of dendritic cells as evidenced Romani. To address

this issue, claim 2 has been amended to include a step requiring differentiating the precursor cell of a dendritic cell into an immature dendritic cell. Neither Jin nor Romani teaches this step. This rejection should be withdrawn as well.

Claim 11 has been amended to incorporate the feature of claim 12. Therefore, this basis of the rejection is now moot.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 1-2 and 8-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Song et al. (US 2002/0123479 A1) in view of Tokusumi et al. (US 6,746,860). For the following reasons, applicants respectfully request reconsideration.

Under 35 U.S.C. § 103(a),

> [a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

The determination of whether an invention would have been obvious under section 103(a) is a legal conclusion based on underlying findings of fact. *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000). The underlying factual inquiries include (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; and (3) the differences between the claimed invention and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). If all the elements of an invention are found in a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (citing *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988)). Both the suggestion and the reasonable expectation of success "must be founded in the prior art, not in the applicant's disclosure." *Id.*

The Patent Office "bears the initial burden of presenting a prima facie case of

unpatentability.... However, when a prima facie case is made, the burden shifts to the applicant to come forward with evidence and/or argument supporting patentability." *In re Glaug*, 283 F.3d 1335, 1338 (Fed. Cir. 2002). Evidence rebutting a prima face case of obviousness can include: "evidence of unexpected results," *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007), and evidence "that the prior art teaches away from the claimed invention in any material respect." *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003. When a patent applicant puts forth rebuttal evidence, the Office must consider that evidence. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (stating that "all evidence of nonobviousness must be considered when assessing patentability.")

For the following reasons, as applied to amended claim 2, the combination of references relied upon by the Office fails to establish a *prima facie* case of obviousness. This is because (1) There was no reasonable expectation that Sendai virus could successfully be used to produce a mature dendritic cell using an immature dendritic cell or a precursor of an immature dendritic cell, and (2) The art of record provides no basis for a reasonable expectation of success with respect to transducing an immature dendritic cell or a precursor of an immature dendritic cell which, in turn, produces mature dendritic cells. Even if it is believed that the Office did make a *prima facie* showing, objective indicia of nonobviousness rebut any *prima facie* case.

In combining Song and Tokusumi, the Office first states at page 7 of the Action:

> Song et al did not teach explicitly the use of a Sendai virus vector for genetically modifying dendritic cells, even though they disclose that the dendritic cells could be genetically modified by any recombinant negative strand RNA virus including any paramyxovirus. [emphasis original]

To overcome the acknowledged deficiencies of Song, the Office relies on Tokusumi, stating at page 8 of the Action:

> it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the teachings of Song et al. by also utilizing the recombinant Sendai virus vector taught by Tokusumi to genetically modify[ ] the dendritic cells for expressing at least a disease associated antigen.

For the following reasons, applicants disagree.

(1) There was no reasonable expectation that Sendai virus could successfully be used to produce a mature dendritic cell using an immature dendritic cell or a precursor of an immature dendritic cell

It is true that Song et al. mention various viruses including astrovirus, coronavirus, orthomyxovirus, papovavirus, paramyxovirus, parvovirus, picomavirus, poxvirus, retrovirus, togavirus, and adenovirus as candidates of gene delivery vehicles (GDVs) (paragraphs 0007 and 0052). But the only virus vector Song et al. has actually demonstrated transducing into dendritic cells is a "retrovirus vector." Although Song et al. further constructed a plasmid encoding a Sindbis virus genome encoding an HBVe antigen sequence (paragraphs 0226 and 0227), there is no clear indication that Song et al. constructed a viral vector using this plasmid. Accordingly, the descriptions of paragraphs 0007 and 0052 of Song et al. cannot be regarded as a scientifically founded disclosure, but should be regarded as a mere desire of Song et al. not based on factual findings.

Moreover, transduction efficiency of dendritic cells shown in Song et al. was extremely low (approximately 0.1 or 0.2%, see paragraph 0173 and 0177).

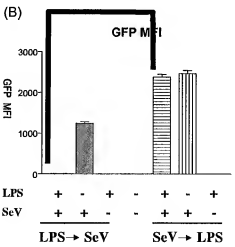
Cremer et al. (*Hum. Gene Ther.* 11:1695-1703, 2000, IDS filed on March 14, 2007; copy enclosed), like Song et al., engineered dendritic cells using retrovirus vector encoding IFN-β. Unlike Song et al., Cremer et al. transduced progenitors of dendritic cells (i.e., $CD34^+$ stem cells). Cremer et al. teach that *"[b]eing averages, these values . . . may mean that <25 or 30% of the cells were transduced"* (page 1697, col. 2, lines 14-16; emphasis added). Cremer et al. further state that, *"dendritic cells (DCs) would not be transformed by this procedure, and one could probably obtain IFN-β-transformed DCs only by transducing stem cell-derived precursors"* (page 1696, col. 1, lines 5-7; emphasis added). Applicants' specification describes that *"in general, the differentiation of the cells to dendritic cells is induced after the introduction of the vectors into CD34-positive cells"* (page 4, lines 15-21; emphasis added).

It is important to point out that transducing dendritic cells using viral vectors is not trivial. There are many potential pitfalls. One cannot reasonably assume that any viral

vector is useful for transducing either dendritic cells or immature dendritic cells or precursors of immature dendritic cells. Even if one virus can be used to transduce a dendritic cell at one particular stage of dendritic cell differentiation, there is no reasonable expectation of success that a different virus, or even a virus of a different class, could be used in the same way.

In the present application, applicants demonstrated that immature dendritic cells are very efficiently infected with Sendai virus vector (82.2 to 95.4%, see values in upper right quadrant in each panels of Fig. 7). The gene transfer efficiency to $CD34^+$ precursor cells was also significantly higher (65 to 70%, see page 46, line 18) in comparison with the result of Cremer et al. as is mentioned above ("<25 or 30%", page 1697, col. 2, lines 14-16).

Applicants also note that such high efficiency gene transduction of Sendai virus vector is not a general feature seen in any cells; it is therefore unexpected. In fact, infectivity of Sendai virus to matured dendritic cells was significantly reduced (Experiment 4). Specifically, mean fluorescence intensity (MFI) of GFP marker expression was incomparably low in matured dendritic cells which were infected with Sendai virus after maturation in comparison with matured dendritic cells which was infected with Sendai virus before maturation (Fig. 9(B), reproduced below).



(Figure 9, panel B)

Such results confirm that the highly susceptible feature of cells to Sendai virus vector

was not known or believed to be generally applicable at the time the present application was filed. Again, even if one viral vector has been used for gene transduction into dendritic cells at one stage of dendritic differentiation, it was unpredictable whether another viral vector can be used under the same conditions. A highly efficient gene transduction specific to immature dendritic cells using Sendai virus vector was an unpredictable finding of the present invention.

Given this unpredictability, and given applicants' experimental results, one skilled in the art would have had no reasonable expectation of success in making the invention by combining the prior art references in question. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988)). ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.").

(2) *The art of record provides no basis for a reasonable expectation of success with respect to transducing an immature dendritic cell or a precursor of an immature dendritic cell which, in turn, produces mature dendritic cells*

While immature dendritic cells have the capacity to take up antigen, immature dendritic cells lose this capacity during the maturation process, becoming capable of antigen presentation and becoming potent stimulators of T-cells as mature dendritic cells. This is confirmed by Kantengwa et al. (*Am. J. Respir. Crit. Care Med.* 167: 431-437, 2003; copy enclosed). Kantengwa et al. state: *"DC [dendritic cell] maturation is a critical process, as only mature DC are able to induce optimal activation of naive T cells"* (See, page 431, col. 2, lines 9-10). Dendritic cell maturation is triggered by, for example, incubation with bacteria, lipopolysaccharide (LPS), or double-stranded RNA (see, for example, page 8, lines 17 of the present specification) or by a specific cytokine cocktail.

The inventors have demonstrated that Sendai virus transduction into immature dendritic cells induces spontaneous maturation of transduced dendritic cells. In other words, immature dendritic cells produce mature dendritic cells without any stimulation (see,

for example, page 46, line 30 through page 47, line 1, Experiment 1). Accordingly, a subsequent maturation procedure using LPS or such can be omitted when transducing immature dendritic cells using Sendai virus vector.

The inventors also found this to be true when dendritic cell precursor cells were transduced with Sendai virus as such cells subsequently differentiated into immature dendritic cells (page 46 lines 9-26, Experiment 6). When transduced precursor cells differentiated into immature dendritic cells, the immature dendritic cells were also subsequently spontaneously maturated. These results indicate that the timing of the infection with Sendai virus vector is not critical to induce spontaneous maturation by the vector. Accordingly, use of Sendai virus has an advantage in that matured dendritic cells are automatically obtained without additional steps.

On the other hand, retroviral gene transduction into dendritic cells did not, in the prior art, induce maturation. For example, Cremer et al., as is cited above, describe that *"[t]he phenotype profile of neo-transduced or IFN-β-transduced DCs resembled the phenotype of immature DCs"* (Paragraph bridging pages 1697-1698). Gasperi et al. (*J. Leukoc. Biol.* 66: 263-267, 1999; copy enclosed) also describe that *"[r]etroviral infection did not modify the immature DC phenotype"* (abstract). Accordingly, spontaneous maturation of dendritic cells using Sendai virus vector is an unpredictable feature identified in the present invention.

A reasonable fact-finder can only conclude that the skilled artisan would not have had a reasonable expectation of success with respect to transducing an immature dendritic cell or a precursor of an immature dendritic cell which, in turn, produces mature dendritic cells. In this case, virus selection is unpredictable, thus rebutting, any reasonable expectation of success in employing Sendai virus in combination with an immature dendritic cell or a precursor of an immature dendritic cell as presently claimed.

(3) *Objective indicia of nonobviousness rebut any prima facie case: unexpected results and teaching away*

Objective evidence of unexpected results exists in this case, rebutting any *prima facie* case for obviousness. The Office must give weight to such evidence of unexpected results. *See Richardson-Vicks, Inc. v. Upjohn Co.,* 122 F.3d 1476, 1483 (Fed.Cir.1997) (evidence of unexpected results must be considered); *Ruiz v. AB Chance Co.,* 234 F.3d 654, 667 (Fed.Cir.2000) ("Our precedents clearly hold that secondary considerations, when present, must be considered in determining obviousness.")

As is discussed above, applicants demonstrated, for the first that immature dendritic cells are readily transduced with Sendai virus vector (82.2 to 95.4%, see values in upper right quadrant in each panels of Fig. 7). The gene transfer efficiency to $CD34^+$ precursor cells was also noted as being significantly higher (65 to 70%, see page 46, line 18) in comparison with the result of Cremer et al. ("<25 or 30%", page 1697, col. 2, lines 14-16). Such data describes an unexpected property or result from the use of a Sendai virus vector as compared to another viral vector.

Such objective evidence are persuasive to overcome any *prima facie* case of unpatentability.

(4) *Summary*

The present inventors have demonstrated that Sendai virus transduction into dendritic cell precursor cells does not disturb, but rather allows, their successive differentiation into immature dendritic cells (page 46 lines 9-26, Experiment 6). The present inventors have also further demonstrated that immature dendritic cells transduced with Sendai virus spontaneously differentiate into mature dendritic cells (Page 46 line 30 to page 47 line 3). Such spontaneous differentiation is advantageous, as it allows transduced cells to differentiate to an immature cell as well as allowing immature dendritic cells to undergo maturation, producing a mature dendritic cell. The present specification further demonstrated that mature dendritic cells generated by transduction with Sendai virus successfully induced potent

allogenic T cell response (Fig. 21), and suppressed tumor growth (Figs. 21 and 23).

Such data, significantly, indicate that the gene transduction with Sendai virus vector into dendritic cell or its precursor causes no apparent adverse effects on the dendritic cell differentiation and function. The claimed transduction system is therefore advantageous for producing transduced mature dendritic cells.

Claims 1-5 were rejected under 35 U.S.C. 103(a) as being unpatentable over Steinman et al. (US 6,300,090) in view of Romani et al. (J. Exp. Med. 180:83-93, 1994). As a feature of claim 9 has been incorporated into claim 2, this ground of rejection is moot. The presently claimed inventions are also nonobvious over Steinman et al in view of Romani et al. for the aforementioned reasons.

Double Patenting

Claims 1-3 and 6-13 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4-8 of copending Application No. 11/630,532. Applicants will address this issue, if appropriate, upon an indication of allowable subject matter.

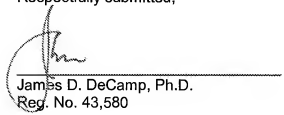
CONCLUSION

Applicant submits that the application is now in condition for allowance, and such action is hereby respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 12/5/2008



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